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Thalassemia

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Thalassemia

A deep insight into causes and diagnosis of Thalassemia

A study by

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The Thalassemias

The Thalassemias are divided into the alpha-Thalassemia , in which the production of alpha- globin that is deficient, and the beta- Thalassemia ; in which beta- globin production is defective.

THE ALPHA-THALASSEMIAS

Alpha- Thalassemias result in the excess production of beta- chains in adults and children

The beta- chains that accumulate forms tetramers – Hemoglobin Barts in infants and hemoglobin H in adults. These tetramers are abnormal hemoglobin with marked instability , a left-shifted oxygen dissociation curve with a lack of co-operability ie. Normal sigmoid shaped. The hematological manifestations of the alpha- Thalassemia are function principally of the extent to which these abnormal tetramers accumulate. This , in turn depends on how many of the four alpha-loci have been deleted or inactivated by mutilation.

THE BETA-THALASSEMIAS

The excess alpha-chains that are formed in beta-Thalassemia don't self associate to form tetramers but instead are bound to the red cell membrane; producing membrane damage. The severity of the beta-Thalassemic defect varies with different mutations. Some mutation prevent the formation of any beta-chains , others allow some beta-chains formation. When both beta-globin genes bear Thalassemic mutation, severe anaemia is present.

Both deletions and point mutations cause this disorder. This causes increase in Erythropoietin and Hepatosplenomegaly may be massive. This causes hemolytic anaemia and bleeding disorder.

Structure of Hemoglobin

Hemoglobin is the red colouring material of blood as it is a component of RBC(Red blood cells). RBC are also called Eryhthrocytes because of presence of Hemoglobin. Hemoglobin belongs to a class of conjugated proteins where heme is the prosthetic group and globin is the protein part.

Hemoglobin = Heme + Globin

Functions of Hemoglobin

1) **In the transport of oxygen from lungs to the tissues and the transport of carbon dioxide from the tissues to the lungs.**
2) **As buffer – The buffering action of hemoglobin is due to amino acid Histidine present in the globin part of hemoglobin. Histidine comprises of 8% of the total amino acid make up of the globin.**

   The presence of hemoglobin increases the oxygen transport capacity of blood. Hemoglobin

plays a vital role in the transport of carbon dioxide and hydrogen ion.

Myoglobin which is located in muscles, serves as a reserve supply of oxygen and also facilitate the movement of oxygen with in muscle.

Heme – Ferrous protoporphyrin is called heme.

Heme is a chelate of ferrous iron with protoporphyrin. Heme is also called protoheme.

Synthesis of heme

The starting material of hemoglobin synthesis are glycine and succinyl coA.

Succinyl coA comes from carbohydrate metabolism.

Glycine comes from amino acid pool of the body.

They combine in the presence of enzymes ; to firm heme(ferrous protoporphyrin).

In mitochondria, oxidative phosphorylation takes place. The mitochondrial ATP are produced hy carbohydrate oxidation. The energy inherent in

the carbohydrate is gradually released during the series of oxidation-reduction reactions.

The glycolysis yields pyruvate (complex carbohydrate breakdown is glycolysis.)

Hence, the oxidation-reduction of pyruvate via the Tricarboxylic Acid(TCA) cycle can generate succinate as well as ethanol at various levels of TCA cycle.

The oxidative decarboxylation of pyruvate to acetyl CoA and Carbon dioxide and of alpha-ketoglutarate to succinyl CoA and carbon dioxide. This is facilitated via the mitochondrial enzymes.

Glycine is amino acid required for heme formation.

In mitochondria, condensation of one glycine and one succinyl CoA by the pyridoxal phosphate requiring enzyme ALAS , can lead to the formation of heme biosynthesis. In the case of loss of ALAS activity in vitamin B6 deficiency , it could cause microchromic microcytic anaemia.

Globin – has 4 polypeptide chains . Two are alpha chains and other two are beta chains.

The four chains are arranged in tetrahedron fashion.

Hemoglobin – 1 molecule of hemoglobin contains 4 heme groups and 1 globin molecule.

The globin moeity is formed from amino acids.

The major amino acid in the globin part of hemoglobin , amongst the amino acid pool from which it is formed , is Histidine.

Histidine(amino acid) is the major part of globin that helps Hemoglobin to carry oxygen.

The myoglobin molecule also has Histidine in globin, thus myoglobin is oxygen carrier too.

Hemoglobin Variants

-are the abnormal mutants of the hemoglobin. These could be formed due to ineffective binding of heme and globin. The globin is synthesised by the transcription and translational reaction as they are globular proteins. Globins are heme

prosthetics groups(that means they can bind to heme)

So, the transcription reaction involves conversion of DNA to RNA.

The initiation of transcription takes place by DNA helix unwinding , then replication of DNA stands by RNA polymerase. The methylation can arrest the replication process.

The RNA polymerase acts on DNA to cause initiation, elongation and termination.

This causes the formation of mRNA (messenger RNA) that contains the codes from DNA. This mRNA is formed inside nucleus, then is transported outside the nucleus to cytoplasm by tRNA (transfer RNA).

Ribosomes are protein synthesising machines in cell. They conduct the task of choosing which amino acid must be added to growing peptide chain by reading successive mRNA codons.

The complex problem of converting the information(mRNA) into product (protein) is

reflected in the elaborate structure of the ribosome. The RNA processing in ribosome via rRNA leads to protein synthesis. Mutations in a single rRNA gene can cause the abnormal protein formation. Abnormal hemoglobin variants are thus produced , that can cause various disease conditions like Thalassemia.

Erythropoiesis is the formation of erythrocytes. The erythropoeitic growth factors are Erythropoietin and Thrombopoeitin.

The bone marrow produces stem cells that eventually become erythrocytes , leucocytes etc. There might be mutations in stem cells produced by bone marrow.

The inheritance of the mutant gene causing tissue-specific patterns of gene expression can cause hematological disease.

Erythropoietin is the major Stimulating factor for erythropoiesis. Iron supply plays a major role in hemoglobin synthesis. The iron released from reticuloendothelial cells can be transported

through the plasma by Transferrin. The erythroid precursors (erythropoietin) uses delivered iron for the synthesis of hemoglobin Erythropoietin, secreted by kidney .

How Thalassemia is caused

When globin synthesis is defective, it causes Thalassemia; which is a hereditary disorder that results in abnormal hemoglobin or insufficient quantity of hemoglobin.

Alpha and Beta globin are products of family of closely related genes. Defects that prevent normal transcription of the gene, splicing of the messenger ; or its translation into protein , all are causes of Thalassemia.

(The defect could either be change in amino acid sequence of globin).

Those abnormalities where there are no abnormal globin chains rather a decrease in the quantity of normal globin chains produced are

called Thalassemia. This causes small and poorly hemoglobinised (ie. Microcytic, hypochromic) red cells.

The amino acid substitution due to mutations can also cause Thalassemia.

Thalassemias can cause abnormal pigmentation accumulation.(methemoglobinemia).

Methemoglobinemia means oxidised hemoglobin with ferric rather ferrous iron or Sulfhemoglobinemia (sulfur is present in porphyrin ring and alters the abiiity to bind oxygen.

Or Carboxyhemoglobinemia (carbon monoxide bound to the heme iron).

The abnormal alpha and beta globin chain cause Alpha-Thalassemia and Beta-Thalassemia.

The clinical feature of Beta-Thalassemia major includes severe hemolytic anaemia and splenomegaly; requires chronic transfusion and suffer iron overload.

The oxidative injury can cause haemolysis in spleen. The Heinz bodies are found in histopathology specimens. The marked coagulation of splenic sinusoids results from this causing marked splenomegaly.

This can cause Porphyrias (group of diseases caused by abnormalities of heme biosynthesis). There is excessive accumulation and excretion of Porphyrins.

Breakdown of hemoglobin can cause bilirubin formation. Bilirubin , in combination with albumen reaches liver, where it undergoes coagulation to form Bilirubin Diglucoronide, which passes bile into the intestines. In the intestines , the Bilirubin Diglucoronide is hydrolysed and bilirubin is converted into urobilinogen. A portion of urobilinogen is absorbed from the intestines to the blood and some is excreted in urine.

The unabsorbed urobilinogen is excreted in stool.

Jaundice is a disease condition characterised by increased concentration of bilirubin.

So, in case of splenomegaly, in Thalassemia; increased breakdown of hemoglobin causes Hemolytic (Prehepatic) Jaundice.

This might cause activation of platelets affecting coagulation of blood.

A routine laboratory test such as hemoglobin electrophoresis can be used for screening of such disorders of hemoglobin.

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